The asbestos minerals are classified according to structural features into two groups, serpentine and amphibole. Chrysotile, a serpentine (white asbestos), comprises pliable, curly fibers that are formed individually from fibrillar subunits. Layers of linked silica tetrahedra alternate with layers of magnesium hydroxide octahedra to form long, hollow, scroll-like structures. Chrysotile accounts for approximately 95 percent of the world usage of asbestos today. The major producers are the Soviet Union and Canada.

The amphibole types of asbestos (crocidolite, amosite, tremolite, actinolite, and anthophyllite) are generally made up of straight, needle-like fibers consisting of strips of silica tetrahedra linked by one or more cations (calcium, sodium, magnesium, and iron). The mineral names are often distinguished by adding the modifier asbestos after the name for those minerals that may occur both as a fiber and not as a fiber. In this text, crocidolite refers to asbestiform richterite and amosite refers to asbestiform grunerite. In the United States, amosite and, to a lesser extent, crocidolite were widely used in the past, but their commercial importance has decreased dramatically in the last two decades (Craighead and Mossman 1982). The amphiboles tremolite, actinolite, and anthophyllite are minor contaminants of some chrysotile and industrial talc products, are present in both asbestiform and nonabestiform types, and are not produced for commercial use.

The occupations and industries in which the major mortality studies of asbestos-exposed workers have been conducted are presented in Table 1. Groups not described in this table, but for whom there is considerable concern about substantial asbestos exposure, include workers in the building and demolition trades and maintenance workers.

The number of workers exposed to asbestos in the United States has been variously calculated, but a detailed review by Nicholson and colleagues (1982) estimated that 18.8 million workers have had more than 2 months of exposure in occupations where significant asbestos exposure may have occurred.

An earlier chapter of this Report documents that age and occupation are associated with substantial differences in smoking behavior. These differences would be expected to substantially alter lung cancer and chronic lung disease mortality; therefore, a careful examination of the smoking habits of asbestos-exposed populations is needed in order to interpret the data on mortality and disease incidence and prevalence reported in the literature. Table 2 presents the smoking habits of asbestos workers from a number of studies of asbestos-exposed populations. In most of the studies of asbestos-exposed populations, approximately 70 to 80 percent of male asbestos workers smoked. In some subsets of workers, well over 90 percent of the individuals were current smokers or had smoked in the past. Li

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TABLE 1.—Mortality from asbestos-related diseases in various cohort studies

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Mining	McDonald et al. (1980)	Quebec	Chrysotile		10,939	3,291	10	42	230	184	125
	Nicholson et al. (1979)	Quebec	Chrysotile		544	178	1	26	28	11.1	252
	Rubino et al. (1979)	Italy	Chrysotile		952	332	0	9	11[1]	10.4	106
	Hobbs et al. (1980)	Western Australia	Crocidolite		6,200	526	17[2]	14	60	38.2	157
	Meurman et al. (1974)	Finland	Anthophyllite	66.7	1,092	248	0	13	21	12.6	167
Friction materials	Berry and Newhouse (1983)	England	Chrysotile Crocidolite[4]		M 9,113 W 4,347	1,640 346	8 2	NS NS	143[3] 6[3]	139.5 11.3	103 53
	McDonald et al. (1984)	Connecticut	Chrysotile Crocidolite[4] Anthophyllite[4]		3,641	1,267	0	12[5]	73	49.1	148.7
General manufacturing	Henderson and Enterline (1979)	United States	Chrysotile Crocidolite Amosite	81	1,075	781	5	31	63[6]	23.3	270.4
	Newhouse and Berry (1979)	England	Chrysotile Crocidolite Amosite		M 2,887 W 693	545 200	46 21	NS NS	103[3] 27[3]	43.2 3.2	238 844

TABLE 1.—Continued

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Textiles	Peto et al. (1977)	England	Chrysotile Crocidolite (?)		1,106	317	10	NS	51[3]	23.8	214
	Peto (1980)	England	Chrysotile Crocidolite (?)		679	239	7	10	40	23.3	172
	Dement et al. (1982)	South Carolina	Chrysotile Crocidolite[4]	52.4	768	191	1	15	26	7.5	348
	McDonald et al. (1983a)	South Carolina	Chrysotile Crocidolite[4]	89[5]	2,543	857	1	21	59	29.6	199.5
	McDonald et al. (1983b)	Pennsylvania	Chrysotile Amosite Crocidolite[4]	75[6]	4,137	1,392	14	74	53	50.5	105
	Robinson et al. (1979)	Pennsylvania	Chrysotile Amosite Crocidolite[4]		M 2,722 W 554	912 128	13 4	NS NS	49 14	36.1 1.7	136 824
Cement products	Weill et al. (1979)	New Orleans	Chrysotile Crocidolite Amosite[4]		5,645	601	0[7]	NS	51	49.2	104
	Finkelstein (1983)	Scarborough	Chrysotile Crocidolite		535	138	19	NS	26	5.4	480
	Thomas et al. (1982)	Cardiff	Chrysotile Crocidolite[4]		1,592	351	2	NS	28	33.0	85
Gas mask manufacturing	Jones et al. (1980)	England	Crocidolite		578	166	17	NS	12	6.3	190
Insulation products	Seidman et al. (1979)	New Jersey	Amosite		820	528	14	30	93	22.8	408

TABLE 1.—Continued

Type of activity	Study	Place	Fiber type	Percent smoking	Number in cohort	Total deaths	Meso-thelioma	Asbestosis (pneumo-coniosis)	Lung cancer		SMR
									Observed	Expected	
Insulators	Newhouse and Berry (1979)	England	Chrysotile Amosite		1,368	83	10	NS	21[3]	5.6	375
	Selikoff et al. (1979)	United States and Canada	Chrysotile Amosite	82.3	17,800	2,271	175	168	486	105.6	480
	Selikoff, Seidman et al. (1980)	New York and New Jersey	Chrysotile Amosite		632	478	38	41	93	13.3	699
Shipyard workers	Rossiter and Coles (1980)	England	Chrysotile Crocidolite Amosite	66.8	6,076	1,043	31	9	84	119.7	70

NOTE: NS, not stated; M, men; W, women.

[1] Includes one suspected case of mesothelioma.

[2] According to the mortality study, which was restricted to deaths before January 1, 1978. The text of this study also noted 26 cases of mesothelioma diagnosed to January 1, 1979.

[3] Pleural mesotheliomas included in lung cancer total given by the authors but taken out of the lung cancer total for the purpose of this Table.

[4] Minimal usage.

[5] Authors stated that none of the cases were clearly attributable to asbestos exposure.

[6] Male eversmokers, 1910–1919 birth cohort.

[7] Two cases did not meet criteria for entry into the cohort.

[8] Includes mesotheliomas.

and colleagues (1983) showed lower rates of smoking among shipyard workers in South Carolina. Only 42.9 percent reported that they were current smokers, and 24.8 percent had ceased smoking. This decline in smoking found in the United States is not evident in studies of asbestos workers in Great Britain.

Lung Cancer

Cigarette smoking is the major cause of lung cancer in the U.S. population considered as a whole (US DHHS 1982). Among U.S. men aged 50 to 70 (the group most commonly examined in occupational mortality studies), over 10 percent of the deaths were due to lung cancer in 1977 (McKay et al. 1982). The prevalence of smoking and the percentage of deaths due to lung cancer vary substantially in the studies of asbestos-exposed populations reported in the literature, but in the largest study (Hammond et al. 1979) of heavily exposed workers with a high smoking prevalence (82.3 percent), 21.4 percent of the deaths were due to lung cancer.

The high incidence of lung cancer in both asbestos-exposed workers and the U.S. population, together with the potency of cigarette smoking in determining lung cancer risk, makes the determination of the smoking habits of asbestos-exposed populations essential to any evaluation of lung cancer. The prevalence of smoking varies markedly among men born in different years of this century, between blue-collar and white-collar workers (see the chapter on smoking patterns), and among the populations of asbestos workers studied in the literature. In particular, men born between 1910 and 1930 have a higher prevalence of smoking than men born earlier; men born after 1930 have had lower prevalences of smoking at any given age than the men born between 1910 and 1930. Levels of asbestos exposure have also not been constant with time. Since the recognition of the hazards of asbestos exposure, improved control of asbestos dust has reduce the levels of asbestos in mines and manufacturing plants and, more recently, in other areas where asbestos exposure may also occur. These temporal trends of smoking prevalence and asbestos dust levels result in complex relationships between cumulative asbestos dust exposure and cumulative smoking exposure. The oldest workers (those born before 1910) may have higher cumulative asbestos dust exposure at any given age than younger workers, but will have a lower smoking prevalence. Workers born between 1910 and 1930 are likely to have both a higher smoking prevalence and a higher cumulative asbestos exposure at any given age than workers born after 1930. Therefore, in many studies of currently employed asbestos workers, cumulative asbestos exposure will be somewhat correlated with smoking prevalence, and biased estimates of dose–response relationships with

TABLE 2.—Smoking characteristics of asbestos-exposed workers

Study	Number and type of population		Smoking characteristics (percent)				Comments
Selikoff et al. (1968)	370 union local members, aged 45–74, New Jersey		SM/EX 76.5	NR* 13	Pipe/cigar 10.5		*Never smoked regularly
Hammond et al. (1979)	17,800 union local members, New Jersey		SM* 54.2	EX 22.2	NS 10.8	Pipe/cigar 5.9	*82.9% smoked >20 cigs/day
Langlands et al. (1971)	252 insulation workers, Belfast	Age <40 years >40 years	69* 74				*19% smoked >25 cigs/day
Ferris et al. (1971)	183 shipyard workers		SM 54.6	NS/EX 45.4			
Murphy et al. (1971)	101 shipyard pipecoverers, New England		SM 66.4	EX 26.8	NS 6.9		
Harries et al. (1972)	2,443 male dockyard workers, Great Britain		64.7	2.2	33.1		
Harries and Lumley (1977)	945 royal naval dockyard workers, Great Britain		67.2	16.2	16.6		
McMillan et al. (1979)	719 royal naval shipyard workers, Great Britain		48.7	28.7	22.7		

TABLE 2.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Kolonel et al. (1980)	Male shipyard workers, Hawaii	Asbestos-exposed workers	63.8			
		Nonexposed workers	62.5			
		General population	58.8			
Pearle (1982)	131 male shipyard workers		75.6			
Li et al. (1983)	3,991 shipyard workers, South Carolina		SM	EX	NS	
			42.9	24.8	32.3	
Becklake et al. (1972)	Asbestos workers, Canada		SM*	NS		*Smokers = ever smoked 1 cig/day for ≥1 yr.; includes pipe and cigar
			85.3	14.7		
Meurman et al. (1973, 1974)	Anthophyllite mine workers, 1936–1967		SM*			*28.1% smoked >15 cigs/day
			66.7			
Liddell et al. (1982)	515 asbestos workers, Quebec			NS		
				33.8		
Berry et al. (1972)	1,203 male asbestos workers		SM	EX	NS	
			74.5	19.5	6	
Meurman et al. (1979)	Asbestos workers, Finland	Cohort survivors	66.7			
		Deceased workers	79.8			

TABLE 2.—Continued

Study	Number and type of population	Smoking characteristics (percent)				Comments
Weill et al. (1975) and Selikoff et al. (1979)	859 asbestos cement mfg. workers, New Orleans	SM 51	EX 26	NS 23		
Greenberg et al. (1976)	890 asbestos workers, Texas	84				
Weiss and Theodos (1978)	40 asbestos workers	55.7*	22.7	21.6		*22.7% smoked >1 pack/day
Berry et al. (1979)	Asbestos textile factory workers, Great Britain	SM 69.2	EX 13.8	NS 17		
Selikoff, Seidman, et al. (1980)	933 amosite asbestos workers, examined 20 yrs. from employment start date	SM 61.7	EX 12.1	NS 13.4	Other 12.6	
Skerfving et al. (1980)	241 asbestos workers, Sweden	64.3				
Weiss et al. (1981)	45 asbestos workers, aged ≥40, reexamined	SM 42.2	EX 31.1	NS 26.7		

TABLE 2.—Continued

Study	Number and type of population		Smoking characteristics (percent)				Comments
				SM	EX	NS	
McDermott et al. (1982)	Two groups of asbestos workers, Swaziland	1	Group	38	10		
		2	Group	33	4		
Acheson et al. (1984)	Amosite asbestos workers, Great Britain			77	5	19	
Berry et al. (1985)	1,253 male and 423 female asbestos factory workers		Men	74.5	19.6	5.9	
			Women	49.4	22.7	27.9	

NOTE: SM = Smoker; EX = Ex-smoker; NS = Nonsmoker.

asbestos may result. These associations between asbestos exposure and smoking must be considered when examining the literature and are particularly important when drawing conclusions from studies that either do not control for smoking or control for smoking inadequately. For these reasons, this discussion is limited largely to those studies that have provided data on the smoking habits of their populations.

Examination of the relationships among smoking, asbestos exposure, and lung cancer includes consideration of a series of separate questions. Does asbestos exposure exert an effect in the absence of active smoking exposure? What are the effects of combined exposure? Is there a threshold of exposure below which no effect occurs? What happens to the risk following smoking cessation and after cessation of new asbestos exposure?

Lung Cancer in Nonsmoking Asbestos Workers

The most direct way to demonstrate that asbestos exposure results in an increased lung cancer risk independent of cigarette smoking is to monitor disease occurrence in asbestos-exposed individuals who have never smoked cigarettes regularly. However, because lung cancer is a relatively rare phenomenon in people who have never smoked cigarettes, even among asbestos-exposed populations, a large population of nonsmokers is required before a statistically significant number of cases would be expected. The relatively high prevalence of smoking in asbestos-exposed populations decreases even further the number of nonsmoking asbestos-exposed workers available for study, making the evaluation of risks for the nonsmokers difficult. For example, no lung cancer deaths were identified among the nonsmokers in the original cohort of asbestos insulation workers reported by Selikoff and colleagues (1968).

Some authors have attempted to increase subject numbers in the nonsmoker category by combining ex-smokers or light smokers with never smokers (Blot et al. 1980). However, the risk of developing lung cancer remains elevated in ex-smokers compared with nonsmokers for at least 10 to 15 years after cessation, and the excess risk is proportionate to the amount smoked (US DHHS 1982). Smokers of less than 10 cigarettes per day have less risk than heavy smokers, but the relative risk for lung cancer in these light smokers compared with individuals who have never smoked regularly still varied from 2.3 to 9.5 in the major prospective studies on smoking mortality (US DHHS 1982). Thus, combining people who have never smoked with ex-smokers and light smokers is inappropriate and may introduce bias when the effects of asbestos exposure alone are being assessed.

Several studies have examined populations large enough to address the question of the risk of asbestos exposure in individuals who have never smoked regularly. Hammond and colleagues (1979)

examined the mortality experience of the 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers who were alive on January 1, 1967. This group was followed to December 1976, and the mortality of the 12,051 workers more than 20 years after onset of exposure was analyzed. Of this group, smoking histories were available for 8,220, of whom 6,841 (83.2 percent) had been regular smokers at some point and 891 (10.8 percent) had never smoked regularly. Of the 891 workers who had never smoked regularly, death certificates indicated that 4 died of lung cancer. The expected number of deaths was calculated from the mortality experience of a population of blue-collar workers who had never smoked regularly, drawn from the American Cancer Society (ACS) prospective mortality study of 1 million men and women. The resulting expected number of lung cancer deaths of 0.7 and the observed number of 4 yielded a relative risk for asbestos exposure of 5.33. When the deaths were classified according to the best estimate of the cause of death from all available data, rather than from the death certificate alone, one additional case of lung cancer was identified in a worker who had never smoked regularly.

Selikoff, Seidman, and Hammond (1980) reported the mortality of 933 men who began working in an amosite asbestos factory between June 1941 and December 1945. Of these men, 78 (8.4 percent) were known to have never smoked regularly; the death certificates of 5 of this group listed lung cancer as the cause of death. When the best estimate of cause of death was used, only three men were believed to have died of lung cancer. The expected number of deaths was 0.2, based on the ACS mortality study. This led to a relative risk of 25 (5/0.2) for workers who had never smoked regularly.

McDonald and colleagues (1980) examined the mortality experience of Quebec asbestos miners and millers and reported a dose–response relationship between cumulative asbestos exposure and lung cancer in nonsmokers. They compared the standardized mortality ratio (SMR) for lung cancer in miners who had never smoked, using the mortality rates for the Province of Quebec, which are based on both smokers and nonsmokers. The SMR increased from 0.18 among nonsmoking miners with less than 30 million particles per cubic foot times years (mppcf•y) of exposure to 0.36 in miners with 30 to 299 mppcf•y of exposure and 1.24 in nonsmoking miners with more than 300 mppcf•y of exposure. There were 19 lung cancer deaths among nonsmoking asbestos miners. These authors (McDonald et al. 1980) also performed a case–control study of the 245 miners who had died of lung cancer. The distribution of cumulative asbestos exposure among the 20 nonsmoking miners with lung cancer and 20 nonsmoking control miners matched for year of birth and smoking status was examined, and the relative risk for lung cancer was found

to have increased from 1 in nonsmoking miners with less than 30 mppcf•y to 10 in nonsmoking miners with more than 1,000 mppcf•y.

Liddell and colleagues (1984) reexamined the same population of Quebec asbestos miners after recording their smoking history by pack-years of exposure. They identified 223 cases of lung cancer in men who worked in the asbestos mines and mills of Quebec for a month or more before January 1967 and who were followed to the end of 1975. The controls were selected from men in the same cohort, born in the same years as the lung cancer cases, but still living. Never smokers represented 23 of the 223 lung cancer cases and 201 of the 715 controls. The relative risks (RR) were calculated on the basis of the mortality experience of the entire asbestos-exposed population (whole population RR, 1.0), and the risk in even the most heavily exposed nonsmokers was still lower than the risk in the entire population, which included both smokers and nonsmokers. The RR for lung cancer increased from 0.19 in the nonsmoking miners who had experienced a cumulative exposure of less than 100 fibers per milliliter times years ((f/mL)y) to 0.37 for those with 101 to 1,000 (f/mL)y and 0.87 for those nonsmoking miners with over 1,000 (f/mL)y, thus demonstrating a dose–response relationship with cumulative asbestos exposure for lung cancer in the workers who had never smoked regularly.

Berry and colleagues (1972) conducted a retrospective study of the lung cancer mortality in more than 1,300 male and 480 female asbestos factory workers over a 10-year period and compared their mortality with the national lung cancer rates (Table 3). The national lung cancer rates were converted to smoking-specific rates by multiplying them by factors from the study of mortality of British physicians by smoking status (Doll and Hill 1964) in order to develop smoking-specific expected numbers of deaths. No lung cancer deaths were recorded among the men who had never smoked, and only one lung cancer death was recorded among the women who had never smoked. The expected number of deaths was also very low, and so even a single death was greater than expected, and it occurred in the group of women with heavy asbestos exposure. The women in the highest asbestos exposure category who had never smoked had 3.5 times the number of subject years at risk when compared with men in the same exposure category (1,404 to 399) owing to the higher prevalence of never-smoker status among women in the study. This difference in number of individuals at risk may have contributed to the demonstration of a lung cancer death among nonsmoking women but not among men. Subsequently, Berry and colleagues (1985) followed prospectively 1,253 male and 423 female asbestos factory workers from the same plants. Smoking habits were determined in 1971 at the start of the study, and the population was followed through 1980. The expected number of lung cancer deaths was

calculated from the death rates for England and Wales multiplied by the lung cancer SMR for greater London, and an adjustment for smoking status was made using the data from the mortality study of British physicians. Observed and expected numbers of lung cancer deaths by smoking status and level of asbestos exposure are presented in Table 4. One lung cancer death occurred among the men who had never smoked (0.1 expected) and three lung cancer deaths occurred among the nonsmoking women (0.2 expected).

Meurman and colleagues (1979) reported 1 lung cancer death (of 23 total lung cancer deaths), a nonsmoking male anthophyllite miner. Acheson and colleagues (1984) also reported 1 death from lung cancer among the nonsmokers employed in an amosite manufacturing factory, with an expected number of 1.1. However, the expected number was calculated from age-specific population rates that included both smokers and nonsmokers rather than from the rates for a population of nonsmokers. Each of these studies supports an increased risk for lung cancer in nonsmoking asbestos workers, but the conclusions are based on a single death in a population.

In summary, the evidence that asbestos exposure results in an increased lung cancer risk in the absence of cigarette smoking is based on a small number of cases, but has been confirmed in several different populations of asbestos workers. The high smoking prevalence in asbestos workers introduces the possibility that environmental tobacco smoke may increase the risk of lung cancer among the nonsmokers, particularly if the synergism demonstrated between active smoking and asbestos exposure pertains to environmental tobacco smoke as well. In spite of these concerns, the available evidence supports the conclusion that nonsmokers with substantial occupational asbestos exposure are at increased risk of developing lung cancer and that the risk increases with increasing cumulative asbestos exposure.

Lung Cancer in Cigarette-Smoking Asbestos Workers

The risk of lung cancer in cigarette smokers has been examined in a number of asbestos-exposed populations, and the increased risk of lung cancer in smokers, coupled with the high prevalence of smoking in many of these populations, has generated substantial numbers of lung cancer deaths for analysis. These populations differ in smoking habits, type of asbestos and duration and intensity of exposure, type of activity that resulted in exposure, and duration of the followup of the population.

A number of authors have compared the lung cancer rates in asbestos-exposed populations with the rates in control populations (Table 1). This approach can establish an excess mortality in a population, but may not identify the causes of that excess. To establish a causal link between an exposure and lung cancer, specific

TABLE 3.—Comparison of number of observed and expected deaths from cancers of the lung

Smoking habits on January 1, 1960	Number of subjects	Subject-years at risk (adjusted)	Observed deaths (all causes)	Observed lung cancer deaths (ICD 162, 163)	Adjusted observed lung cancer deaths	Expected lung cancer deaths
Men						
Low/moderate asbestos exposure						
Never smoked	44	376	2	0	0	0.0
Ex-smokers	38	335	1	0	0	0.1
Smokers	509	4,423	32	8(2)[1]	4.6	6.2
Not known	219	2,122	20	0	3.4	2.0
Severe asbestos exposure						
Never smoked	41	399	11	0	0	0.0
Ex-smokers	39	415	3	2	1.6	0.2
Smokers	663	6,920	82	32(5)	25.5	9.9
Not known	281	2,722	29	4	10.9	2.4
Women						
Low/moderate asbestos exposure						
Never smoked	25	271	8	0	0	0.0
Smokers	45	577	6	1	1	0.3
Not known	19	195	0	0	0	0.1
Severe asbestos exposure						
Never smoked	120	1,404	23	2(1)	1.7	0.2
Smokers	292	3,474	52	18(4)	15.5	1.4
Not known	157	1,547	9	0	2.8	0.4

[1] Figures in parentheses indicate number of pleuralmesotheliomas.

SOURCE: Berry et al. (1972).

TABLE 4.—Observed and expected deaths from cancer of the lung during 1971–1980

Smoking habits in 1971	Number of subjects	Subject-years at risk	Total deaths	Lung cancer deaths	
				Observed	Expected[1]
Men					
Low/moderate asbestos exposure					
Never smoked	45	396	6	1	0.10
Ex-smokers	123	1,092	18	3	1.07
Smokers	441	3,557	84	17	11.29
Severe asbestos exposure					
Never smoked	29	273	2	0	0.06
Ex-smokers	123	1,003	38	8	1.25
Smokers	522	4,394	135	35	14.63
Women					
Low/moderate asbestos exposure					
Never smoked	17	128	5	0	0.04
Ex-smokers	12	93	3	0	0.09
Smokers	27	220	4	0	0.32
Severe asbestos exposure					
Never smoked	101	799	26	3	0.20
Ex-smokers	84	659	24	2	0.50
Smokers	182	1,413	52	10	2.02

[1] Calculated after allowing for the effect of smoking, sex, age, period, and region.

SOURCE: Berry et al. (1985).

criteria must be applied to the entire body of information available on the exposure. This approach has been carefully and comprehensively followed for both cigarette smoking (US DHHS 1982) and asbestos exposure (Selikoff and Lee 1978), and the evidence is sufficient to establish a causal role for both of these agents in producing lung cancer. This section confines itself to an examination of their interaction.

Selikoff and colleagues (1968) were the first to demonstrate increased lung cancer risk among asbestos workers in an investigation that assessed smoking habits. In a group of 370 asbestos insulation workers, none of the 48 workers who had never smoked regularly or of the 39 workers who smoked only pipes or cigars developed lung cancer. Of the 283 cigarette-smoking workers, 24 died of lung cancer during the 4 years and 4 months of the followup period, although only 2.98 lung cancer deaths were expected on the basis of smoking-specific death rates.

A more extensive evaluation of the risk of cigarette smoking for asbestos insulation workers was provided (Hammond et al. 1979) by a prospective evaluation of the 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers discussed earlier. Of this population, 8,220 workers were more than 20 years beyond their onset of asbestos exposure and had a known smoking status. Fifty-four percent of this group were cigarette smokers at the start of the study. The comparison group was drawn from the ACS study of 1 million men and women, and consisted of 73,763 white men with no more than a high school education and not employed as farmers, but with a history of occupational exposure to dust, fumes, vapors, gases, chemicals, or radiation, who were living on January 1, 1967, and were traced thereafter. The control group was followed only until September 30, 1972, and the asbestos workers were followed through 1976; therefore, the lung cancer death rates in the control group were adjusted upward to reflect changes in the U.S. national mortality experience for lung cancer during the time period of differential followup.

There were 1,332 deaths among workers more than 20 years after onset of exposure whose smoking habits were known; 314 (23.6 percent) deaths were due to lung cancer, using the best estimate of cause of death. Death certificate data indicated 272 lung cancer deaths. Figure 2 portrays the mortality ratios for smokers and nonsmokers in the control and the asbestos-exposed populations, with the mortality ratio of nonsmokers in the control group set at 1. The lung cancer death rates increased from 11.3 per 100,000 among nonsmokers in the control group to 58.4 in the nonsmoking asbestos workers, 122.6 for smokers in the control group, and 601.6 for smoking asbestos workers. The lung cancer relative risk with combined exposure (53.24) is far larger than the sum of the

individual risks for cigarette smoking and asbestos exposure separately, and is quite close to the product of the separate mortality ratios (5.17 and 10.85) together.

Accurate data on the intensity of asbestos exposure for individual workers (dose) were not available for this group of insulation workers, and so an asbestos dose–response relationship was not examined. Dosage data were available for cigarette smokers in this population, however, and the ratio of observed to expected lung cancer deaths (with the expected deaths calculated from the rates in nonsmoking non-asbestos-exposed controls) increased from 5.33 in asbestos workers who never smoked regularly to 7.02 in pipe and cigar smokers, 36.56 in ex-smokers, 50.82 in smokers of fewer than 20 cigarettes per day, and 87.36 in asbestos workers who smoked one pack or more per day.

Interaction between smoking and asbestos exposure in the development of lung cancer has also been explored in other populations. In some studies the numbers have been too small to clearly differentiate between an additive and a multiplicative effect with combined exposure; however, the data have been consistent with an effect that is at least more than additive. This interaction of cigarette smoking and asbestos exposure has been demonstrated in asbestos factory workers (Berry et al. 1972, 1985), Quebec miners and millers (McDonald et al. 1980; Liddell et al. 1984), amosite asbestos factory workers (Selikoff, Seidman, and Hammond 1980) and Finnish anthophyllite miners and millers (Meurman et al. 1979).

A dose–response relationship between cigarette smoking and lung cancer in the general population has been readily demonstrated in a number of prospective mortality studies (US DHHS 1982); however, dose–response relationships for asbestos exposure and lung cancer have been more difficult to establish. The carcinogenicity of asbestos may vary with the type of asbestos, and possibly with the length or diameter of the fiber. There are also potential differences in the carcinogenic risk associated with the different stages and processes of converting asbestos from the raw mineral in the mine into a finished manufactured product. As a result, it is difficult to classify the asbestos exposure of different study populations with a single measurement that quantifies the carcinogenic dose. Even if such a scale were agreed upon, actual measurements of asbestos dust levels in the work environment are often not available. Measures of dust exposures for individual workers are even less frequently available. The quantification of asbestos dust exposure has frequently used estimates of likely exposures based on work conditions and job classification, rather than actual measurements of asbestos dust in the air, because of the absence of these measurements for most workers. This lack of information has been particularly problematic for workers employed more than 20 years ago, a group now at high

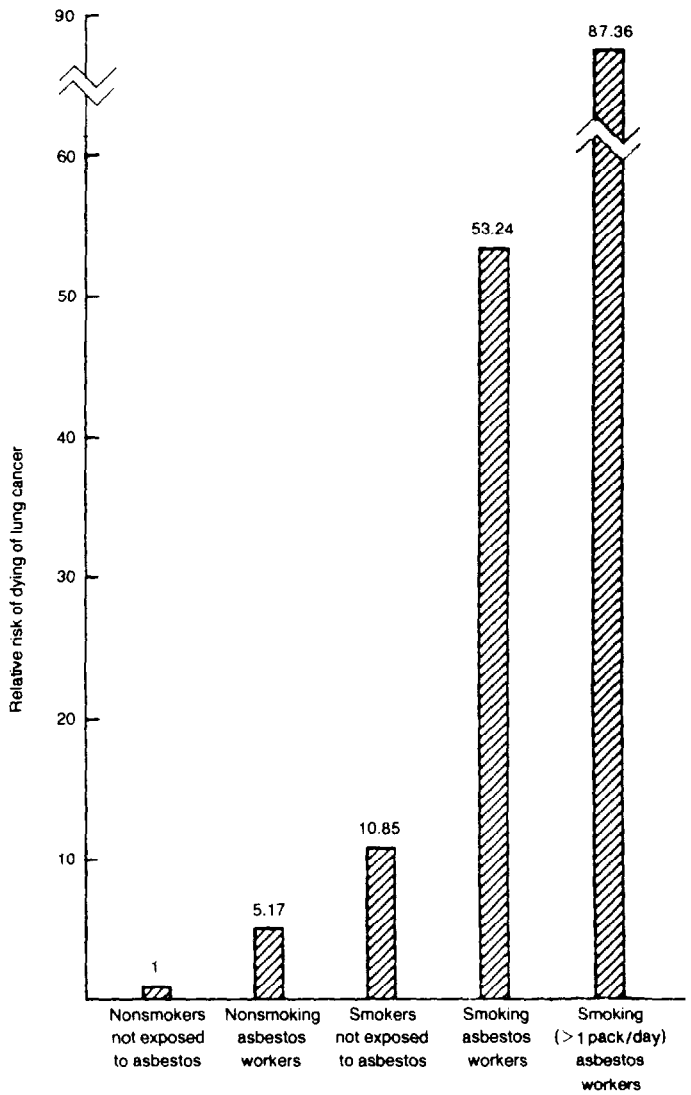

FIGURE 2.—Relative risk of dying of lung cancer for smoking and nonsmoking asbestos workers and smoking and nonsmoking control group members

SOURCE: Hammond et al. (1979).

risk of developing lung cancer. Finally, cumulative asbestos exposure, age, and cumulative cigarette smoking exposure are generally

correlated. Older employees worked under conditions of much higher asbestos exposure than their younger counterparts, and these same older cohorts probably also had higher prevalences of cigarette smoking, as described in the chapter on smoking patterns by occupation. Confounding between cumulative asbestos exposure and cumulative cigarette smoke exposure may result when dose–response relationships between cumulative asbestos exposure and lung cancer are examined without a control for differences in smoking habits among the different asbestos exposure groups.

Berry and colleagues (1972) examined dose–response relationships in a population of 1,300 male and 480 female asbestos factory workers in Great Britain. Workers were categorized as having low to moderate asbestos exposure or severe asbestos exposure, and the expected number of lung cancer deaths was calculated from standardized mortality rates for lung cancer for the greater London area. An adjustment for cigarette smoking status, derived from the mortality study of British physicians by Doll and Hill (1964), was used to estimate rates for smokers and nonsmokers. The results are presented in Table 3. The small number of lung cancer deaths makes interpretation somewhat difficult, but it appears that the increased lung cancer death rate is limited to smokers with severe asbestos exposure.

McDonald and colleagues (1980) examined Quebec miners and presented evidence for a dose–response relationship between cumulative asbestos exposure and lung cancer risk in the smoking miners. They compared the lung cancer mortality rates in the Quebec miners with the mortality rates for the Province of Quebec. Table 5 shows the SMRs for lung cancer in miners by level of cumulative asbestos exposure and smoking habits. Heavy smokers consistently had higher SMRs than moderate smokers at the same level of cumulative asbestos exposure, and the SMRs increased with increasing cumulative exposure to asbestos in each of the smoking categories. Using the same population of miners, these authors conducted a case–control study of 245 lung cancer victims and a similar number of control miners matched for smoking habits and year of birth. The distribution of cumulative asbestos dust exposure was examined, and the results in cigarette smoking miners showed an increase in relative risk with increasing cumulative exposure. The relative risk of cigarette smokers in the lowest exposure category (< 30 mppcf•y) was set at 1.0, and the relative risk increased to 1.12 at 30 to 300 mppcf•y of exposure, 1.58 at 300 to 1,000 mppcf•y, and 1.99 at $\geq 1{,}000$ mppcf•y of exposure.

A more quantitative description of the smoking habits of the same Quebec miners was provided by Liddell and colleagues (1984). Their data are presented in Table 6. The dust exposure measurements were made as particles per cubic foot with midget impingers, and

TABLE 5.—Deaths from lung cancer in relation to dust exposure and smoking habit

	Dust exposure (mppcf•y) accumulated to age 45							
	<30		30–299		≥300		All	
Smoking habit	0	SMR	0	SMR	0	SMR	0	SMR
Nonsmokers	5	0.18	6	0.36	8	1.24	19	0.38
Moderate smokers	73	1.14	64	1.35	52	2.31	189	1.41
Heavy smokers	13	2.12	11	2.39	10	4.50	34	2.63
All smoking habits	91	0.93	81	1.18	70	2.25	242	1.23

SOURCE: Liddell et al. (1984)

individual exposures were calculated on the basis of the work histories and the measurements of impinger dust counts in the work environment between 1949 and 1966. These counts were then converted to fibers per mL. Two hundred and twenty-three cases of lung cancer were identified and matched to 715 controls born in the same year, and a case–control analysis was conducted. As is shown in Table 6, the relative risk of developing lung cancer increases with increasing asbestos exposure category for each of the cumulative pack-year categories. The analysis also suggests that the interaction between cigarette smoking and asbestos exposure is greater than additive.

Thus the studies that have examined the question of a dose–response relationship for asbestos exposure and lung cancer in the face of an adequate control for cigarette smoking have shown an increasing risk of lung cancer as asbestos exposure increases. This suggests that a dose–response relationship for asbestos exposure and lung cancer does exist, and that it is not explained by differences in smoking habits.

Threshold

The question whether a level of asbestos exposure exists below which an exposure does not result in an increased risk of lung cancer is one that is both technically extremely difficult to answer and extremely important to those required to make policy with regard to asbestos exposure. Current understanding of carcinogenesis and host defenses against cancer are not advanced sufficiently to allow either the acceptance or the rejection of a threshold. It is common practice to assume a linear relationship between the dose of a carcinogen and the development of carcinoma, and to assume that the dose–response relationship does not have a threshold. The linear nonthreshold model allows the extrapolation of data obtained for higher exposures

TABLE 6.—Risks of lung cancer, by cigarette smoking and asbestos exposure, relative to all 223 cases and 715 referents for whom smoking histories were reliable; unmatched analysis

Pack-years[1]		Exposure accumulated up to 9 years before death of case (f mLy)			
		Low (< 100)	Medium (< 1,000)	High and very high (≥ 1,000)	All
0	Number of cases	6	7	10	23
	Number of referents	103	61	37	201
	Relative risk	0.19	0.37	0.87	0.37
1, < 40	Number of cases	29	27	34	90
	Number of referents	123	93	63	279
	Relative risk	0.76	0.93	1.73	1.03
≥ 40	Number of cases	40	35	35	110
	Number of referents	117	79	39	235
	Relative risk	1.10	1.42	2.88	1.50
All	Number of cases	75	69	79	223
	Number of referents	343	233	139	715
	Relative risk	0.70	0.95	1.82	1.00

[1] Number of cigarettes a day/20 x duration in years.
SOURCE: Liddell et al. (1984).

to the very low exposures. This extrapolation is substituted for the examination of the very large populations that would have to be examined in order to demonstrate the small expected excess risk with low dose exposure. Such models are particularly attractive for exposures for which human epidemiologic data are limited or absent. As discussed earlier, however, minimal exposure to cigarette smoke and asbestos is probably a nearly universal experience in urbanized society. Because of the large population exposed, more careful examination of the available evidence on the risks of these exposures is necessary.

The number of cigarettes smoked per day by an individual is a readily available measure of the dose of smoke exposure in the active cigarette smoker; therefore, it has been possible to examine relatively completely the dose–response relationship for cigarette smoking and lung cancer. There is a consistent increased risk for lung cancer among smokers in the lowest category of number of cigarettes smoked per day in the major prospective mortality studies on smoking (US DHHS 1982). In the study of U.S. veterans (Kahn 1966), a relative risk for lung cancer of 3.77 was demonstrated in those who smoked only occasionally compared with those who had never smoked regularly (the relative risk for those who smoked 1 to 9 cigarettes per day was 4.07 compared with those who never smoked

regularly). It seems clear that for the active cigarette smoker there is no safe cigarette and no safe level of cigarette smoking (US DHHS 1982). Furthermore, recent data (IARC, in press) suggest that repetitive exposure to environmental tobacco smoke may be accompanied by an increased risk of lung cancer, thereby suggesting that the dose–response relationship may extend even to those individuals who do not actively smoke cigarettes.

The quantification of asbestos exposure is far more difficult. One method is to quantitatively estimate the number of asbestos fibers in digested lung tissue. Asbestos fibers are demonstrable in the lungs of the majority of urban dwellers (Churg and Warnock 1977); however, the number of fibers per gram of lung tissue in urban dwellers without known asbestos exposure is usually several orders of magnitude below that found in occupationally exposed workers, and the type of asbestos varies as well. Churg and Warnock (1979) assessed this urban asbestos exposure as a risk factor for lung cancer by comparing the number of asbestos bodies in 103 patients with lung cancer compared with the number in control patients matched for age, sex, smoking habits, and in some cases, occupation. No differences in the number of asbestos bodies per gram of lung tissue were found between the lung cancer patients and the control population, suggesting that, at this level of exposure, asbestos did not increase the risk of lung cancer in these patients. However, the small number of patients in this study limits the power of the study to find a small effect of asbestos lung burden on lung cancer risk.

Confounding by cigarette smoking is another potential source of bias in evaluating the effects of low levels of asbestos exposure. Several of the studies presented in Table 1 do not show excess lung cancer risks at low levels of asbestos exposure, a pattern consistent with the existence of a threshold. However, lung cancer rates in the general population are determined largely by smoking habits, and if the asbestos-exposed populations have even modestly lower lifetime smoking rates, the effect of asbestos exposure may be masked. This bias is of particular importance at the relatively low levels of asbestos exposure at which the effect of cigarette smoking would be expected to predominate. Thus, in interpreting standardized mortality ratios at or below 1, careful consideration must be given to confounding by the smoking habits of the workforce before concluding that the levels of asbestos exposure experienced by these populations do not result in an increased lung cancer risk. In addition, modest differences in the number of cigarettes smoked per day or the age of initiation of regular smoking between the exposed population and the population from which the SMR is derived could counterbalance a modest risk due to asbestos exposure even in populations with similar smoking prevalences.

For lung cancer, the measurement of a threshold in epidemiologic studies is further constrained by the certainty with which the absence of an effect can be established. The precision and the accuracy of an estimation of the expected number of deaths in a workforce is heavily influenced by the detail with which the smoking behaviors are determined and the accuracy with which the lung cancer risk of a given smoking history can be estimated.

In the U.S. population during 1977, 10 percent of the men who died between the ages of 50 and 70 died of lung cancer (McKay et al. 1982). Therefore, a workforce with smoking patterns similar to the U.S. population would be expected to have a similar mortality experience, in the absence of any asbestos exposure. A 10 percent increase in the risk of lung cancer in a workforce (SMR 110, RR 1.1) due to asbestos exposure would mean that 1 percent of the deaths among workers aged 50 to 70 would be excess lung cancers due to asbestos, a level of risk unacceptable as the basis for an industrial hygiene standard. However, even with carefully determined smoking histories for a worksite, no data are currently available that would allow the calculation of expected death rates in smokers and nonsmokers with precision sufficient to establish that an increase of 10 percent was not simply an error in the estimates. In addition, estimates of the smoking habits of the U.S. population are not known with enough precision to adjust national or regional death rates for the smoking patterns of a given workforce so that a 10 percent difference could be considered significant. The result is a dilemma for those who would try to measure a threshold level, or an "acceptable" exposure level, for occupational exposure to asbestos: an effect too small to measure in statistical terms is still too large to be acceptable in human terms.

A final caution in the determination of a threshold for lung cancer risk secondary to asbestos exposure, and in the use of such a threshold to establish environmental dust standards, is the potential differences between a threshold for lung cancer and one for mesothelioma or other asbestos-related disease. Mesothelioma, which is not associated with cigarette smoking, may occur following exposure to low levels of asbestos, and a level of dust exposure defined as a "safe" level for lung cancer risk may possibly continue to produce an increased risk of mesothelioma.

A pragmatic approach to the problems of defining a threshold or establishing safe levels has been to define asbestos exposure standards on the basis of the lowest level of asbestos dust exposure that can be produced with existing technology. This approach reduces the risk, but does not answer the question whether the exposure of a worker is "safe."

An alternate approach has been to use the existing exposure–response data. In the face of uncertainty about the shape of the

exposure–response curve for asbestos exposure and lung cancer and whether a threshold exists, an assumption that asbestos has a linear exposure–response relationship with lung cancer and no threshold for effect has been suggested as both reasonable and a way to set standards (Peto 1979; NRC 1984). By definition, in this approach there can be no "safe" level of exposure (i.e., no threshold), only an "acceptable" degree of risk. However, using this method, once an "acceptable" level of lung cancer in a working population has been defined, the level of asbestos exposure that would result in that level of risk can be estimated. A corollary of this approach is that asbestos is assumed to contribute to the lung cancer that develops in populations of workers who have been exposed to asbestos regardless of their level of exposure; by extension, the asbestos found in the lungs of urban dwellers with no known occupational asbestos exposure is assumed to make a small (but finite and definable) contribution to all lung cancers. The evidence that does exist (Churg and Warnock 1977) suggests that asbestos exposure makes no "measurable" contribution to lung cancer in individuals without a definable exposure, but it is impossible to establish the absence of "any" effect.

If the issues of liability can be separated from the issue of threshold, then the problem of reducing and eliminating asbestos-related disease and disability could be approached with a broader focus. The focus could be expanded beyond improving technology for reducing exposure to asbestos to include other methods of reducing the cancer risk associated with asbestos exposure. If the goal is to reduce the lung cancer deaths associated with asbestos rather than simply reducing the levels of asbestos dust in the worksite, then the deaths due to the interaction between smoking and asbestos must be dealt with, and the elimination of smoking will be a potent adjunct to environmental asbestos dust control in this task, particularly for those workers who have already received substantial asbestos exposure. A public health "feasibility" threshold could then be defined, not in terms of what dust levels were achievable, but rather in terms of what lung cancer death rates were achievable. This threshold would be the lowest cancer risk achievable, given our current technology, and would include minimizing asbestos exposure, maximizing smoking cessation, and applying techniques for early diagnosis and treatment.

In summary, although the level of asbestos exposure that occurs in the general population does not appear to be accompanied by an increased risk of lung cancer, the demonstration of a clear threshold below which there is no effect in occupationally exposed populations is not possible.

TABLE 7.—Lung cancer mortality ratios with cessation of cigarette smoking in male smokers who smoked more than 20 cigarettes per day compared with those who never smoked regularly

Years since cessation	Not exposed to asbestos[1]	Asbestos insulation workers[2]
Current smokers	11.69	10.4
Under 1 year	17.7	
1–4 years	10.1	11.5
5–9 years	6.5	4.2
≥10 years	1.8	3.4
Never smoked regularly	1	1

[1] Data from Hammond (1972).
[2] Data from Hammond (1979).

Cessation of Exposure

A decline in the relative risk of developing lung cancer following cessation of cigarette smoking was demonstrated in cigarette-smoking asbestos workers by Hammond and colleagues (1979). Table 7 shows the lung cancer mortality ratios in asbestos workers who are current smokers and who have quit for varying periods of time, compared with those workers who have never smoked regularly. A companion set of numbers is provided of the relative risks for lung cancer in men not exposed to asbestos, but who are current smokers or have quit for varying periods of time, derived from the American Cancer Society study of 1 million men and women (Hammond 1972).

Several authors have attempted to approach the question of the risk of lung cancer following cessation of asbestos exposure by examining the relative risks of asbestos exposure in workers following retirement (Walker 1984; Selikoff, Hammond et al. 1980). The data in Figure 3 and Table 8 reveal that the relative risk for lung cancer in asbestos workers increases and then declines with the increasing number of years from initial exposure. The workers with the longest interval from onset of exposure are also of the greatest age within the populations examined. Because of this link with age, the interpretation of this decline in relative risk as indicating that cessation of asbestos exposure results in a decline in lung cancer risk must be made with great caution. Examination of national age-specific mortality rates for lung cancer (Figure 4) also shows a decline in male lung cancer death rates with increasing age. This decline with age is an artifact of the cross-sectional nature of data